

What is claimed is:

1. A matrix comprising:

a substrate capable of providing attachment of a heparin-binding peptide;  
a peptide comprising a binding domain that binds heparin with high affinity;  
heparin or a heparin-like polymer; and  
a protein growth factor or peptide fragment thereof having a domain that binds heparin with low affinity.

2. The matrix of claim 1 wherein the growth factor or peptide fragment thereof that binds heparin with low affinity is further defined as eluting from a heparin-affinity column at a NaCl concentration of about 25 mM to about 140 mM.

3. The matrix of claim 1 wherein the domain of the growth factor or peptide fragment thereof is further defined as comprising a length of about 8 to 30 amino acid residues comprising at least 2 basic amino acid residues, a ratio of basic to acidic amino acid residues of at least 2, and a ratio of hydrophobic amino acid residues to basic amino acid residues of at least 0.67.

4. The matrix of claim 3 wherein the basic amino acid residue is K or R.

5. The matrix of claim 3 wherein the acidic amino acid residue is further defined as D or E.

6. The matrix of claim 3 wherein the hydrophobic amino acid residue is further defined as A, V, F, P, M, I, or L or C when C is involved in a disulfide bond.

7. The matrix of claim 1 wherein the growth factor or peptide fragment thereof is neurturin, persephin, IGF-1A, IGF-1 $\beta$ , EGF, NGF $\beta$ , NT-3, BDNF, NT-4, TGF- $\beta$ 2, TGF- $\beta$ 3, or TGF- $\beta$ 4.

8. The matrix of claim 7 wherein the growth factor or peptide fragment there is further defined as neurturin or a peptide fragment thereof.
9. The matrix of claim 7 wherein the growth factor or peptide fragment thereof is further defined as persephin or a peptide fragment thereof.
- 5 10. The matrix of claim 7 wherein the growth factor or peptide fragment thereof is further defined as IGF-1A or a peptide fragment thereof.
11. The matrix of claim 7 wherein the growth factor or peptide fragment thereof is further defined as IGF-1 $\beta$  or a peptide fragment thereof.
12. The matrix of claim 7 wherein the growth factor or peptide fragment thereof is  
10 further defined as EGF or a peptide fragment thereof.
13. The matrix of claim 7 wherein the growth factor or peptide fragment thereof is further defined as NGF $\beta$  or a peptide fragment thereof.
14. The matrix of claim 1 wherein the growth factor or peptide fragment thereof is further defined as NT-3 or a peptide fragment thereof.
- 15 15. The matrix of claim 1 wherein the growth factor or peptide fragment thereof is further defined as BDNF or a peptide fragment thereof.
16. The matrix of claim 1 wherein the low heparin-binding affinity growth factor protein or peptide fragment thereof is further defined as NT-4 or a peptide fragment thereof.
- 20 17. The matrix of claim 1 wherein the low heparin-binding affinity growth factor protein or peptide fragment thereof is further defined as TGF- $\beta$ 2 or a peptide fragment thereof.

18. The matrix of claim 1 wherein the low heparin-binding affinity growth factor protein or peptide fragment thereof is further defined as TGF- $\beta$ 3 or a peptide fragment thereof.

19. The matrix of claim 1 wherein the low heparin-binding affinity growth factor protein or peptide fragment thereof is further defined as TGF- $\beta$ 4 or a peptide fragment thereof.

20. The matrix of claim 1 wherein the substrate comprises fibrin.

21. The matrix of claim 1 wherein the substrate comprises a synthetic polymer hydrogel.

22. The matrix of claim 1 wherein the peptide comprising a domain that binds heparin with high affinity is further defined as eluting from a heparin-affinity column at not less than 140 mM NaCl.

23. The matrix of claim 1 wherein the peptide comprising a domain that binds heparin with high affinity is further defined as comprising SEQ ID NO: 1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID No:4, or SEQ ID NO:5.

24. The matrix of claim 1 wherein the heparin or heparin-like polymer has a molecular weight between about 3,000 and 10,000,000 Daltons.

25. The matrix of claim 1 wherein the heparin-like polymer is a polysaccharide having a molecular weight between about 3,000 and 10,000,000 Daltons, and having at least one negative charge per two saccharide rings and no more than one positive charge per ten saccharide rings.

26. The matrix of claim 1 wherein the heparin-like polymer is dextran sulfate, chondroitin sulfate, heparan sulfate, fucan, alginate, or a derivative thereof.

27. The matrix of claim 1 wherein the molar ratio of heparin or heparin-like polymer to growth factor is at least one.
28. The matrix of claim 1 wherein the molar ratio of covalently attached peptide having a binding domain that binds heparin with high affinity to heparin or a heparin-like polymer is at least one.
29. A matrix comprising:
- a substrate capable of providing attachment of heparin or a heparin-like polymer;
  - heparin or a heparin-like polymer; and
  - a growth factor or peptide fragment thereof having a domain that binds heparin with low affinity.
30. The matrix of claim 29 wherein the low heparin-binding affinity of the growth factor protein or peptide fragment thereof is further defined as eluting from a heparin-affinity column at a NaCl concentration of about 25 mM to about 140 mM.
31. The matrix of claim 29 wherein the growth factor protein or peptide fragment thereof comprises of a domain length of about 8 to 30 amino acid residues comprising at least 2 basic amino acid residues, a ratio of basic to acidic amino acid residues of at least 2, and a ratio of hydrophobic amino acid residues to basic amino acid residues of at least 0.67, which growth factor protein further elutes from a heparin-affinity column at a NaCl concentration less than about 140 mM.
32. The matrix of claim 29 wherein the growth factor or a peptide fragment thereof is further defined as neurturin, persephin, IGF-1A, IGF-1 $\beta$ , EGF, NGF $\beta$ , NT-3, BDNF, NT-4, TGF- $\beta$ 2, TGF- $\beta$ 3, TGF- $\beta$ 4, or a peptide fragment thereof having a domain that binds heparin with low affinity.

33. The matrix of claim 29 wherein the growth factor or a peptide fragment thereof is further defined as neurturin or a peptide fragment thereof having a domain that binds heparin with low affinity.
34. The matrix of claim 29 wherein the growth factor or a peptide fragment thereof is further defined as persephin or a peptide fragment thereof having a domain that binds heparin with low affinity.
35. The matrix of claim 29 wherein the growth factor or a peptide fragment thereof is further defined as IGF-1A or a peptide fragment thereof having a domain that binds heparin with low affinity.
- 10 36. The matrix of claim 29 wherein the growth factor or peptide fragment thereof is further defined as IGF-1 $\beta$  or a peptide fragment thereof having a domain that binds heparin with low affinity.
37. The matrix of claim 29 wherein the growth factor or peptide fragment thereof is further defined as EGF or a peptide fragment thereof having a domain that binds heparin with low affinity.
- 15 38. The matrix of claim 29 wherein the growth factor or a peptide fragment thereof is further defined as NGF $\beta$  or a peptide fragment thereof having a domain that binds heparin with low affinity.
39. The matrix of claim 29 wherein the growth factor or a peptide fragment thereof is further defined as NT-3 or a peptide fragment thereof having a domain that binds heparin with low affinity.
- 20 40. The matrix of claim 29 wherein the growth factor or a peptide fragment thereof is further defined as BDNF or a peptide fragment thereof having a domain that binds heparin with low affinity.

41. The matrix of claim 29 wherein the growth factor or a peptide fragment thereof is further defined as NT-4 or a peptide fragment thereof having a domain that binds heparin with low affinity.
42. The matrix of claim 29 wherein the low heparin-binding affinity growth factor or a peptide fragment thereof is further defined as TGF- $\beta$ 2 or a peptide fragment thereof having a domain that binds heparin with low affinity.
43. The matrix of claim 29 wherein the growth factor or a peptide fragment thereof is further defined as TGF- $\beta$ 3 or a peptide fragment thereof having a domain that binds heparin with low affinity.
- 10 44. The matrix of claim 29 wherein the growth factor or a peptide fragment thereof is further defined as TGF- $\beta$ 4 or a peptide fragment thereof having a domain that binds heparin with low affinity.
45. The matrix of claim 29 wherein the substrate comprises fibrin.
46. The matrix of claim 29 where the substrate comprises collagen.
- 15 47. The matrix of claim 29 wherein the substrate comprises hyaluronic acid or a hyaluronic acid derivative.
48. The matrix of claim 29 wherein the substrate comprises a synthetic polymer hydrogel.
49. The matrix of claim 29 wherein the heparin or heparin-like polymer has a  
20 molecular weight between about 3,000 and 10,000,000 Daltons.
50. The matrix of claim 29 wherein the heparin-like polymer is a polysaccharide having a molecular weight between about 3000 and 10,000,000 Daltons and having at least one negative charge per 2 saccharide rings and no more than 1 positive charge per 10 saccharide rings.

51. The matrix of claim 29 wherein the heparin-like polymer is dextran sulfate, chondroitin sulfate, heparan sulfate, fucan, alginate, or a derivative thereof.

52. The matrix of claim 29 wherein a molar ratio of heparin or heparin-like polymer to growth factor or a peptide fragment thereof is included in the matrix of at

5 least 1.

53. A matrix comprising:

a substrate capable of supporting the attachment of a cell, wherein said substrate comprises heparin or a heparin-like polymer bound thereto; and

growth factor or a peptide fragment thereof having a domain that binds heparin with

10 low affinity,

wherein under physiological conditions the low heparin-binding affinity growth factor is released by degradation of a component of the matrix or by dissociation of the growth factor from the heparin or heparin-like polymer.

54. The matrix of claim 53 wherein the substrate comprises fibrin.

15 55. The matrix of claim 53 wherein the heparin or heparin-like polymer is non-covalently attached to the substrate.

56. The matrix of claim 53 wherein the heparin or heparin-like polymers is covalently attached to the substrate.

57. A vascular graft comprising a matrix capable of supporting cell adhesion, said  
20 matrix comprising bound heparin or heparin-like polymer and a growth factor having low binding affinity for heparin.

58. An article for treatment of dermal wounds comprising a matrix capable of supporting cell adhesion, said matrix comprising bound heparin or heparin-like polymer and a growth factor having low binding affinity for heparin.

Rev 5  
Add  
cont'd

59. The article of claim 58, wherein the growth factor is TGF- $\beta$ 3.

60. An article of manufacture comprising a matrix capable of supporting cell adhesion, said matrix comprising bound heparin or heparin-like polymer and a growth factor or peptide fragment thereof having low binding affinity for heparin.

5 61. An implantable sterilized composition comprising a matrix capable of supporting cell adhesion, said matrix comprising bound heparin or a heparin-like polymer and a growth factor or peptide fragment thereof having low binding affinity for heparin.

62. A method for providing controlled release of growth factor comprising:

10 preparing a matrix comprising a growth factor having a domain with low affinity for binding heparin and bound heparin or heparin-like polymer; and  
placing the matrix on a wound in need thereof.

63. The method of claim 62, wherein the growth factor is released by degradation of a component of the matrix or by dissociation of the growth factor from the heparin

15 or heparin-like polymer.

Rev  
A 7

5  
10  
15  
20  
25  
30  
35  
40  
45  
50  
55  
60  
65  
70  
75  
80  
85  
90  
95  
100

add  
A 10